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Secondary Somatic Mutations Restoring RAD51C and RAD51D Associated with Acquired Resistance to the PARP Inhibitor Rucaparib in High-Grade Ovarian Carcinoma  


Précis: In patients with high-grade ovarian carcinoma treated with the PARP inhibitor rucaparib, secondary reversion mutations in HR genes restore the open reading frame and HR activity to confer resistance.  

See commentary, p. 937  
See article, p. 1006  

Analysis of Circulating Cell-Free DNA Identifies Multiclonal Heterogeneity of BRCA2 Reversion Mutations Associated with Resistance to PARP Inhibitors  


Précis: Multiclonal BRCA2 reversion mutations were detected in circulating cell-free DNA from two patients with metastatic prostate cancer after PARP inhibitor treatment, suggesting a mechanism of resistance.  

See commentary, p. 937  
See article, p. 984  
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Circulating Cell-Free DNA to Guide Prostate Cancer Treatment with PARP Inhibition  


Précis: Sequencing cfDNA from patients with olaparib-treated prostate cancer reveals that reduced cfDNA is a biomarker of response and can harbor resistance mutations that may guide treatment.  

See commentary, p. 937  
See article, p. 984  
See article, p. 999  

Ibrutinib Unmasks Critical Role of Bruton Tyrosine Kinase in Primary CNS Lymphoma  


Précis: The BTK inhibitor ibrutinib has activity in patients with relapsed or refractory B-cell lymphomas of the CNS, and dual treatment with PI3K/mTOR inhibitors may enhance ibrutinib efficacy in patients with CD79B-mutant tumors.  

See commentary, p. 940  

Discovery and Optimization of HKT288, a Cadherin-6-Targeting ADC for the Treatment of Ovarian and Renal Cancers  


PARP inhibitors (PARPi) have demonstrated activity in patients with mutations in homologous recombination (HR) genes such as BRCA1 and BRCA2. Three related studies identified HR gene reversion mutations that confer resistance to PARPi. Kondrashova and colleagues discovered secondary reversion mutations in BRCA1, RAD51C, and RAD51D in patients with PARPi-resistant ovarian cancer. Similarly, Quigley, Alumkal, and colleagues identified BRCA2 reversion mutations associated with PARPi resistance in circulating cell-free DNA (cfDNA) from two patients with prostate cancer. Finally, Goodall, Mateo, and colleagues found secondary reversion mutations in BRCA2 and PALB2 in cfDNA from patients with PARPi-resistant metastatic prostate cancer. Together, these studies demonstrate that HR gene reversion mutations can promote resistance to PARPi. For details, please see the article by Kondrashova and colleagues on page 984, the article by Quigley, Alumkal, and colleagues on page 999, and the article by Goodall, Mateo, and colleagues on page 1006.